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ORIGINAL ARTICLE

Gender differences in the prognostic impact of chronic kidney disease in patients with left ventricular systolic dysfunction following ST elevation myocardial infarction treated with primary percutaneous coronary intervention

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Abstract *Background/Aim:* Renal function potentially has different prognostic impact in men and women with acute myocardial infarction. The aim of this study was to evaluate the prognostic impact of chronic kidney disease (CKD) on five-year all-cause mortality in men and women with left ventricular systolic dysfunction (LVSD) following ST elevation myocardial infarction (STEMI).
Method: We included 348 consecutive STEMI patients who were treated with primary percutaneous coronary intervention (pPCI) and had a left ventricular ejection fraction < 40%. CKD was defined as baseline creatinine clearance (CrCl) < 60 ml/min. Patients with cardiogenic shock at admission were excluded.
Results: Among analyzed patients, 104 patients (29.8%) were women, and 244 patients (70.1%) were men. Compared with male patients, female patients were older. Females were more likely to have previous angina and hypertension. CKD was more common in women compared with men (54.8% *vs.* 22.5%, p<0.001). Female gender and older age were independent

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predictors of CKD. No significant difference in five-year all-cause mortality was between men and women (27.8% *vs.* 23.3%, p=0.370). In a Cox regression model (adjustments were made for age, Killip class at admission, post-procedural flow TIMI<3, left main stenosis and women with diabetes), CKD remained an independent predictor of five-year all-cause mortality in men (HR 2.2; 95% CI 1.22–3.3, p=0.007).

Conclusions: Although pre-terminal CKD was more frequently noted in women, it was an independent predictor of five-year mortality exclusively in men. Different prognostic significance of CKD between sexes indicates that renal function must be considered in the prognosis of men and women following acute myocardial infarction.

1. Introduction

Even in mild forms, chronic kidney disease (CKD) is a well-known risk factor for adverse cardiovascular outcomes in patients with ST elevation myocardial infarction (STEMI) and left ventricular systolic dysfunction (LVSD).[1–3] Over the past several decades, increasing knowledge regarding sex differences in coronary heart disease has emerged.[4] Several studies suggest that the prevalence of risk factors, pathophysiology, clinical manifestation and prognosis of coronary heart disease vary between men and women.[4–8] CKD is more prevalent among women with coronary artery disease; however, female patients are generally older and have more comorbidities compared with men.[9–11] Certain studies have shown that CKD has a different prognostic impact on short-term and mid-term mortality following STEMI in women and men,[9,10] i.e., in patients with angiographically proven coronary disease.[11] The results of some of these studies have shown that CKD is an independent predictor of mortality following STEMI exclusively in women.[10] In contrast, other studies suggest that CKD is an independent predictor of mortality in both sexes but exhibits a negative prognostic significance in men.[9] Patients with LSVD following STEMI represent a group with a high risk of mortality, and this risk is additionally increased by the presence of CKD.[1–3,12] The combined presence of CKD and LVSD is the most important independent predictor of one-year overall mortality after pPCI.[13] To the best of our knowledge, the prognostic significance of CKD in women and men with LVSD after acute myocardial infarction has not been analyzed to date.

The objective of this study is to evaluate the prognostic value of renal function on long-term mortality in men and women with left ventricular systolic dysfunction following STEMI.

2. Method

2.1. Study population, data collection and definitions

In the present study, data from the prospective Clinical Center of Serbia STEMI Register for a subgroup of 348 consecutive patients with LVSD hospitalized between February 2006 and April 2008 were used. The purpose of the prospective Clinical Center of Serbia STEMI Register has been published elsewhere.[14] In brief, the objective of the register is to gather complete and representative data on the management and short- and long-term outcomes of patients with STEMI undergoing primary PCI at our centre. The local research ethics committee approved the study protocol. All consecutive patients with STEMI aged 18 or older who were admitted to the Coronary Care Unit after undergoing pPCI at our centre were included in the register. For the purpose of this study, patients with cardiogenic shock at admission were excluded. Coronary angiography was performed via the femoral approach. Primary PCI and stenting of the infarct-related artery (IRA) was performed according to the standard technique. Aspirin (300 mg) and clopidogrel (600 mg) were administered to all eligible patients before pPCI. Selected patients with visible intracoronary thrombi were also administered the GP IIb/IIIa receptor inhibitor tirofiban during pPCI. Flow grades were assessed according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. After pPCI, patients were treated according to current guidelines.

Demographic, baseline clinical, angiographic and procedural data were collected and analyzed. The baseline CKD was defined as creatinine clearance (CrCl) < 60 ml/min/m^2 at admission.[15] Creatinine clearance was calculated using the Cockrof-Gault formula:

$$CrCl = ((140\text{-years})*\text{body weight})/(72*\text{creatinine in mg/dl}).$$

The value was multiplied by 0.85 in females.

Echocardiographic examination was performed within the first three days after pPCI. The left ventricular ejection fraction (LVEF) was assessed according to the biplane Simpson method, in classical two- and four-chamber apical projections. LVEF<40% was considered as LVSD. LVEF was absent in 10% of patients. The missing data were imputed via the single imputation method.

Patients received follow-up for five years after enrolment. Follow-up data were obtained by scheduled telephone interviews and outpatient visits.

2.2. Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD) if the distribution was normal or as the median (med) with 25th and 75th quartiles (IQR) if the distribution was skewed. Categorical variables were expressed as frequency and percentage. Analysis for normality of data was performed using the Kolmogorov-Smirnov test. Baseline differences between groups were analyzed using the Student t-test (if the distribution was normal) or the Mann-Whitney test (if the distribution was skewed) for continuous variables and the Pearson X^2 test for categorical variables. Multivariable logistic regression was used to define independent predictors of CKD, and the Cox regression model (backward method, with $p < 0.10$ for entrance into the model) was used to identify independent risk factors for five-year all-cause mortality. The Kaplan–Meier method was used to construct the probability curves for five-year survival, whereas the difference between the groups was assessed using the Log-Rank test. SPSS statistical software version 14.0 was applied (SPSS Inc., Chicago, IL).

3. Results

Out of a total of 348 patients, 104 (29.8%) were women, and 244 (70.2%) were men. Compared with men, women were older and had a higher prevalence of previous angina and hypertension, but they were less likely to be smokers. Regarding renal function, 54.8% of women and 22.5% of men had CrCl<60 ml/min/m^2. The demographic characteristics, risk factors, previous cardiovascular diseases or procedures, characteristics on admission, renal function, angiographic, procedural characteristics and therapy at discharge in relation to gender are presented in Table 1.

The female gender and (older) age were independent predictors of CKD [female gender OR 4.11 (95% CI 2.11–7.97), p<0.001; age (years) OR 1.21 (95% CI 1.16–1.26), p<0.001].

During hospitalization, a lethal outcome was registered in 18 (17.3%) women and 39 (15.9%) men (p= 0.760). A lethal outcome within the first 30 days was registered in 20 (19.3%) women and 43 (17.6%) men (p=0.721). During the five-year follow-up, a lethal outcome was registered in 29 (27.8%) women and 57 (23.3%) men (p=0.370).

Deteriorating renal function was associated with increasing five-year mortality in both men and women, as presented in Fig. 1.

Table 2 presents the unadjusted and adjusted hazard ratios (95% confidence interval) for all-cause mortality during follow-up (Cox regression model) according to gender. In the Cox regression model for five-year all-cause mortality, adjustments were made for the following variables: age (years), heart failure at admission, diabetes, three-vessel disease and postprocedural TIMI flow grade <3.

After adjusting variables defined in the univariate analysis as predictors of mortality, CKD remained an independent predictor of all-cause mortality during a five-year follow-up in men but not in women, as shown in Table 2.

4. Discussion

The results of the present study confirmed that patients with LVSD following STEMI who had a reduced CrCl had an increased five-year mortality rate compared with patients with preserved kidney function. In both men and woman, the lower the CrCl, the higher the mortality rate. No statistically significant difference in five-year mortality between men and women was noted. CKD was more often noted in women. CKD was a strong predictor of five-year mortality in both sexes in the univariate analysis. However, after multivariate adjustment, CKD remained an independent predictor of mortality exclusively in men.

Differences in survival between women and men with acute myocardial infarction have been reported in various studies.[16–18] In other studies, the differences in survival disappear after adjustments for age, comorbidity, and other differences in baseline characteristics between sexes.[8,19–22] In addition, data demonstrate a difference in survival between men and women upon myocardial infarction during short-term follow-up. In contrast, during long-term follow-up (greater than one year), the survival in women and men is approximately identical.[19,23] Although no difference was registered in the present study regarding short-term and long-term mortality between men and women, the independent predictors were different, i.e., they had a different prognostic significance.

To date, two studies have analyzed the prognostic impact of CKD on mortality in men and women with STEMI who underwent primary PCI,[9,10] but no studies are available comparing the prognostic impact of CKD in men and women with LVSD following STEMI. The study by Damman et al. that analyzed approximately 2,000 patients reported that decreased kidney function is associated with increased 30-day mortality and long-term mortality (3 years) in men and women treated with pPCI.[9] Similar to the present study, baseline kidney function was assessed using the Cockroft-Gault formula.[9] This study reported that women were older, more frequently suffered from hypertension, and smoked less frequently smokers. In addition, the parameters of kidney function (eGFR) were reduced in women compared with men, and these findings are consistent with our findings.[9] The value of estimated glomerular filtration (eGFR) <60 ml/min was a strong independent predictor of mortality in both women and men; however, an increased hazard ratio for mortality at 30-day and three-year follow-up was registered in men.[9] This difference in the independent and negative influence of reduced eGFR values remained even after adjustment for other independent mortality predictors (mortality predictors from the TIMI score and by adding biomarkers NT-pro BNP, glucose, and cardiogenic shock).[9] In the present study, the independent and negative predictive influence of CKD in women disappeared after adjusting for variables that were predictors of five-year mortality defined in the univariate analysis. In contrast to the present study, a study by Lawesson et al. found that reducing eGFR every 10 ml/min was an independent predictor of mortality and major adverse cardiovascular events (MACE) during one-year follow-up exclusively in women treated with pPCI.[10] This study also observed CKD more frequently in

Table 1 Baseline characteristics and therapy at discharge of the study patients according to gender.

Characteristics	Women (N=104)	Men (N=244)	p-value
Age, years med (IQR)	67.5 (65, 70)	57 (51, 67)	<0.001
Previous MI, n (%)	13 (12.5)	56 (22.9)	0.025
Previous AP, n (%)	17 (16.3)	11 (4.5)	<0.001
Previous PCI, n (%)	1 (0.9)	12 (4.9)	0.055
Previous stroke, n (%)	6 (5.7)	17 (6.9)	0.681
Diabetes, n (%)	29 (27.8)	55 (22.5)	0.286
Hypertension, n (%)	80 (76.9)	154 (63.1)	0.012
HLP, n (%)	65 (62.5)	145 (59.4)	0.592
Smoking, n (%)	36 (34.6)	135 (55.3)	<0.001
Pain duration, hours med (IQR)	4.75 (2.5, 7.0)	3 (2, 5)	0.529
HF at admission, n (%)	41 (39.4)	77 (31.5)	0.156
Systolic BP (mmHg) at admission, X±SD	133.8±29.13	129.7±35	0.257
HR at admission, X±SD	82.7±18.15	80.8±21.8	0.357
Door to balloon time, minutes, med (IQR)	120 (86, 170)	125 (85, 180)	0.900
three-vessel disease, n (%)	33 (31.7)	92 (37.7)	0.288
Pre-procedural flow TIMI 0, n (%)	67 (64.4)	158 (64.7)	0.321
LM stenosis, n (%)	9 (8.7)	22 (9)	0.954
IIb/IIIa blockers, n (%)	51 (49)	135 (55.3)	0.321
Stent implantation, n (%)	94 (90.4)	221 (90.6)	0.956
Postprocedural flow TIMI<3, n (%)	14 (13.5)	24 (9.8)	0.351
Acute stent thrombosis, n (%)	1 (0.9)	4 (1.7)	0.193
LVEF (%), X±SD	36.4±5.65	35.4±6.54	0.148
CKmax, med (IQR)	2406 (1272,3565)	2890 (1506, 4927)	<0.001
Troponin I (μg/L) med (IQR)	15 (12.8, 17,6)	25 (9.5, 19.6)	<0.001
Creatinine μmol/L med (IQR)	67.5 (57, 73)	97 (86, 105)	<0.001
CrCl ml/min med (IQR)	65 (57, 73)	84 (68, 106)	<0.001
CrCl>60 ml/min	47 (45.1)	189 (77.4)	<0.001
CrCl 45–60 ml/min	34 (32.8)	35 (14.4)	<0.001
CrCl<45 ml/min	23 (22.1)	20 (8.2)	<0.001
Therapy at discharge			
Aspirin, n (%)	101 (97.6)	240 (98.7)	0.609
Clopidogrel, n (%)	102 (98)	238 (97.5)	0.990
Beta blockers, n (%)	77 (74)	195 (79.9)	0.061
ACE inhibitors, n (%)	74 (71.1)	175 (71.7)	0.953
Statins, n (%)	77 (74.1)	186 (76.2)	0.660
Diuretics, n (%)	60 (57.6)	142 (58.2)	0.597
Antiarrhythmics, n (%)	7 (6.7)	11 (4.6)	0.376
Digitalis, n (%)	3 (2.8)	5 (2.4)	0.622
Warfarin, n (%)	6 (5.7)	22 (9.1)	0.316

AP=angina pectoris; HLP=hyperlipidaemia; MI=myocardial infarction; HF=heart failure; BP=arterial blood pressure; HR=heart rate; LM=left main coronary artery; CK=creatinine kinase; CrCl=creatinine clearance; LVEF= left ventricular ejection fraction; ACE-=angiotensin converting enzyme.

women,[10] which was also attributed to age and an increased frequency of hypertension and/or diabetes mellitus. However, even after adjusting these variables, the female sex remained an independent predictor of CKD; females exhibited a 5-fold increased risk of CKD compared with males.[10]

The differences in the prognostic impact of CKD between women and men were reported in other studies analyzing patients with coronary disease but not patients with a decreased ejection fraction. A smaller study including patients who suffered from acute coronary syndrome revealed that an elevated creatinine value at admission to hospital was an independent predictor of long-term mortality in women but not in men.[24] A study by Chen et al. analyzing consecutive patients referred for coronagraphy (data from the Appropriateness of Coronary Revascularization (ACRE) Study) reported that mild and moderate CKD were stronger independent predictors of long-term mortality in women compared with men.[11]

The difference in the prognostic significance of CKD in women and men with coronary disease has not been completely explained; the different prevalence of risk factors for coronary disease, CKD and mortality were noted as the possible reason for this being the case.[9,10,20,25] Women with coronary disease are generally older and are more prone to CKD, and the value of CrCl decreases with age. In addition, the simultaneous presence of multiple risk factors for coronary disease, CKD, and mortality (e.g., diabetes mellitus, hypertension, etc.) is thought to be more common in women.[9,20] When the characteristics of women

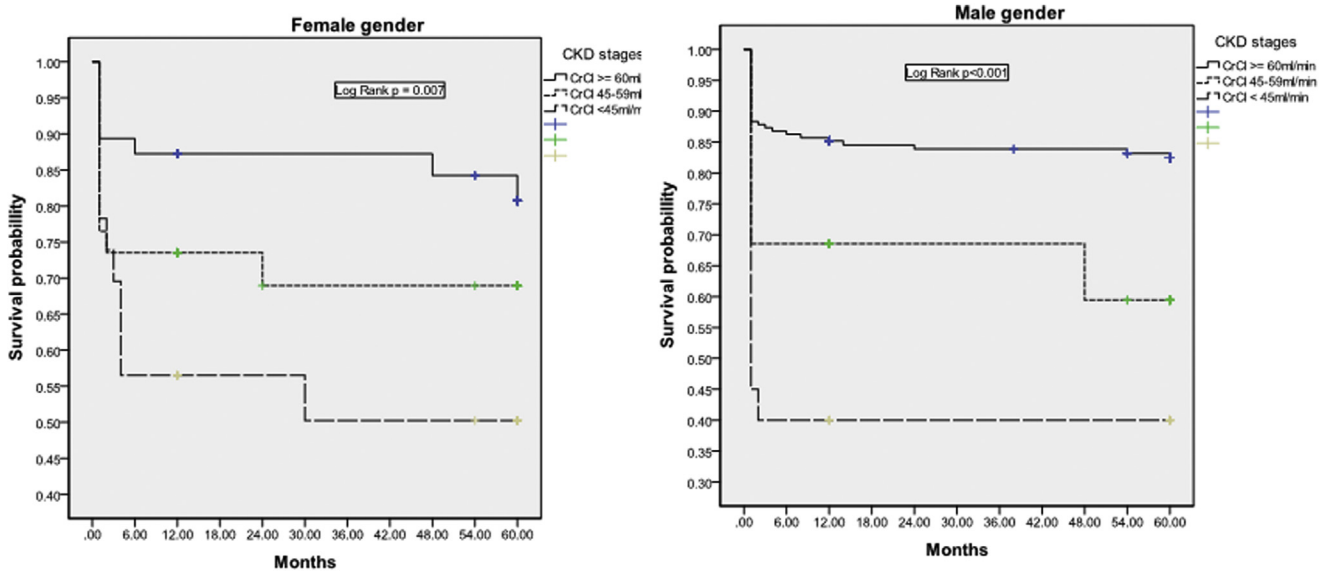

Figure 1 Kaplan–Meier curves estimating the probability of five-year mortality according to gender and renal function.

Table 2 Unadjusted and adjusted hazard ratios (95% confidence interval) for five-year all-cause mortality according to gender.

Variable	Women HR (95% CI)	p-value	Men HR (95% CI)	p-value
Unadjusted HR				
CrCl<60 ml/min	2.4 (1.1–5.4)	0.037	3.0 (1.8–5.1)	<0.001
Adjusted HR				
CrCl<60 ml/min	1.4 (0.6–3.7)	0.495	2.2 (1.2–3.3)	0.007
CrCl 45–60 ml/min	1.1 (0.4–2.7)	0.912	1.8 (0.9–3.7)	0.054
CrCl < 45 ml/min	2.1 (0.8–4.8)	0.817	2.8 (1.4–4.9)	<0.001
Age (years)	1.1 (1.0–1.2)	<0.001	1.01 (1.0–1.06)	0.006
Postprocedural flow TIMI<3	4.1 (1.8–9.2)	0.001	2.6 (1.4–4.9)	0.004
HF at admission	2.2 (1.1–4.8)	0.040	2.9 (1.7–5.1)	<0.001
Three-vessel disease	ns		1.7 (1.1–2.9)	0.048

CrCl = creatinine clearance; HF = heart failure; ns = non significant.

and men with intact kidney function (CrCl>60 ml/min) were compared, men with CrCl>60 ml/min generally exhibited more favourable baseline characteristics compared with women with CrCl >60 ml/min.[9,10] However, even after multivariate adjustment of most of the known variables that may be associated with an increased risk of CKD, the female sex continues to be an independent predictor of CKD.[10] Renal dysfunction is associated with anaemia, endothelial dysfunction, elevated homocysteine levels, procoagulation status, systemic inflammation, and hyperparathyroidism. However, these factors are typically not routinely noted in everyday clinical practice or studies, including the present one. The difference between these characteristics in men and women cannot be excluded, and the differences could be the reason for the different prognostic impact of CKD.[4,9–11] Finally, some authors suggest that the difference in the prognostic impact of CKD between the sexes could be caused by differences in treatment for women and men with myocardial infarction, which primarily involve less frequent application of therapy with a favourable influence on survival, e.g., ACE inhibitors and beta blockers.[4,10,19] The present study did not register a difference in prescribed therapy between women and men at the time of hospital release or during follow up, so this factor cannot be deemed the cause of the different prognostic impact of CKD. However, our study was not designed to analyze the influence of therapy on survival. Nevertheless, gender differences in the prognostic impact of CKD in men and women with coronary artery disease require further investigation.[10]

5. Conclusion

In this single-centre study, no gender differences in five-year all-cause mortality were noted in patients with left ventricular systolic dysfunction following STEMI. Although pre-terminal CKD was more frequently noted in women, it was exclusively an independent predictor of five-year mortality in men. This result requires confirmation using a larger number of patients with more events. The different prognostic significance of CKD between sexes indicates that renal function must be considered in the prognosis of men and women following acute myocardial infarction.

6. Study limitations

This is an observational prospective study, but it included consecutive patients, thus limiting possible selection bias. Data from follow-up echocardiographic examinations obtained while monitoring of patients with LVSD are not available to assess whether a certain degree of recovery of myocardium contractility occurred. On the other hand, the coincidence of CKD potentially influenced the deterioration of systolic function and left ventricle remodelling.[26] Renal function was not evaluated during follow-up. However, during the five-year follow-up, terminal renal insufficiency did not occur, and none of the patients started haemodialysis. Renal function was assessed using the Cockroft-Gault formula,[27,28] which also has limitations.

Disclosure statement

The authors report no financial relationships or conflicts of interest regarding the content herein.

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